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1 **NEUROPHYSIOLOGICAL ANALYSIS**
 2 **OF CIRCADIAN RHYTHM ENTRAINMENT**

3
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ABSTRACT

1
2 We review recent studies in our laboratory which have investigated the neural
3 mechanisms underlying photic entrainment of the mammalian circadian system. The results
4 from studies of extracellular single-unit recordings and of photic induction of Fos-like
5 immunoreactivity (-lir) indicate that excitatory amino acid (EAA) transmission, and particularly,
6 activation of the NMDA receptor subtype, is important for conveying photic information to
7 suprachiasmatic nucleus (SCN) cells. We have also found that a sub-region of the SCN still
8 shows Fos-lir after blockade of EAA receptors, and we have evidence suggesting that these
9 cells are innervated by a distinct subdivision of the retinal projection to the SCN. In addition,
10 we have found that photic responses of cells in the intergeniculate leaflet (which projects to the
11 SCN) and of SCN cells are modulated by serotonin via a receptor that resembles the 5HT_{1A}
12 subtype.

13

1 The goal of our research program is to understand the physiological mechanisms
2 underlying photic entrainment of the mammalian circadian system. Light information reaches
3 the mammalian circadian pacemaker exclusively via the paired retinae and is conveyed through
4 the optic nerves to two structures in the diencephalon: the suprachiasmatic nucleus (SCN) in
5 the hypothalamus and the intergeniculate leaflet (IGL) in the thalamus (Moore, 1973;
6 Harrington et al., 1985). Anatomical studies have demonstrated that the SCN is innervated at
7 least in part by retinal ganglion cells that also project to the lateral geniculate nuclei (Millhouse,
8 1977; Pickard, 1985). Cells in the IGL and adjacent parts of the ventral lateral geniculate
9 nuclei, in turn, project to the SCN, forming the geniculohypothalamic tract (GHT); some of the
10 cells forming the GHT contain neuropeptide Y (NPY); others contain enkephalin, and there are
11 probably also other unidentified transmitters (Card and Moore, 1989; Harrington et al., 1985;
12 Morin et al., 1992). Cells in and near the SCN also project back to the IGL region of the
13 geniculate (Morin et al., 1992), so these structures are richly interconnected via both direct and
14 indirect routes.

15 One of our approaches to understanding the physiology of photic entrainment involves
16 extracellular recordings of SCN and IGL cell firing rates in both *in vitro* slice preparations from
17 hamsters and rats and in anesthetized intact animals. Another approach involves studying the
18 photic regulation of SCN cell gene expression and its pharmacological basis.

19

20 **EXCITATORY AMINO ACIDS**

21 Neurophysiological studies of responses of SCN cells to light have indicated that SCN
22 cells respond to diffuse retinal illumination sluggishly and often with sustained changes in
23 firing rates (Groos and Mason, 1980; Meijer et al., 1986). Although sustained changes in
24 firing-rates in response to sustained changes in illumination are characteristic of both SCN and
25 IGL cells (as tested with durations of over 1 h for some IGL cells), they differ in their response
26 latencies (Meijer et al., 1986; Harrington and Rusak, 1989). In one sample, SCN cells
27 showed average latencies to respond to illumination of 61.4 ± 7.4 (SEM) ms ($n=7$), while IGL

1 cells showed latencies of 4.2 ± 0.8 ms ($n=10$) (S.-W. Ying, unpublished observations). SCN
2 cells also show graded responses to increasing total luminance reaching the eyes, with
3 responses beginning at high thresholds and saturating 2-3 log units above threshold (Meijer et
4 al. 1986; Meijer and Rietveld, 1989). These cells, therefore, seem to function as luminance
5 detectors, tracking intensity changes with firing rate changes, and maintaining these firing rates
6 at stable levels over long intervals.

7 We have also recorded from SCN cells in slices maintained *in vitro* and have examined
8 the effects of putative transmitters on firing rates to see if any of these mimic the known effects
9 of light on SCN cells. A number of studies have suggested that an excitatory amino acid
10 (EAA) is involved in mediating photic input via the direct retinohypothalamic tract (RHT)
11 projection to the SCN, as appears also to be the case for other parts of the visual system
12 (Shibata et al. 1986; Liou et al, 1986; Cahill and Menaker, 1989; Colwell et al., 1990; Kim and
13 Dudek, 1991). We examined the effects of lengthy applications of EAA transmitters on SCN
14 cells and found that glutamate activated most cells, as did kainate and quisqualate, which are
15 agonists for the AMPA receptor, but for some cells responses declined during continuous
16 application of these agonists. The selective agonist N-methyl-D-aspartate (NMDA) also
17 activated SCN cells and did so in a sustained, dose-dependent fashion, which mimicked the
18 sustained responses of SCN cells to photic input in the whole animal. Activation of SCN cells
19 by NMDA could be attenuated by co-application of the selective, competitive NMDA antagonist
20 APV, but it had little effect on kainate-induced activations (Mason and Rusak, 1991).

21 Electrical stimulation of the chiasm underlying the SCN in the slice preparation also
22 activated SCN cells and this effect was also attenuated by APV treatment. This result suggests
23 that sustained activation of the SCN via the optic nerves depends on an NMDA-regulated ion
24 channel. This conclusion appears to contradict the conclusions from field potential studies
25 (Cahill and Menaker, 1989) and intracellular studies (Kim and Dudek, 1991) of SCN
26 responses to optic nerve stimulation. In the intracellular study, Kim and Dudek (1991) found
27 that excitatory postsynaptic potentials in SCN cells evoked by optic nerve stimulation are

1 mediated primarily by non-NMDA mechanisms, with only a small, late component being
2 sensitive to an NMDA antagonist.

3 In fact, there is no contradiction between these findings, since the intracellular and field
4 potential studies monitored transient potentials evoked by single, very brief (0.15 or 0.5 ms)
5 stimulations of the optic nerves. By contrast, we used continuous drug applications, electrical
6 stimulation or photic input (*in vivo*) lasting from many seconds to several minutes in our
7 studies, which probably more closely mimic the time course of entraining stimuli. The
8 transient evoked potentials mediated by non-NMDA mechanisms probably function as a gating
9 mechanism that allows continued photic input to act through slower, voltage-dependent NMDA
10 channels to permit sustained changes in SCN cell firing rates. Similar conclusions have been
11 reached for cells in the lateral geniculate nuclei (cf. Sillito et al., 1990). NMDA channels
12 appear to play a role once neurons have been partially depolarized (Kim and Dudek, 1991),
13 which could happen via the rapid activation of non-NMDA receptors. It is, however, the
14 sustained activation of SCN cells through an NMDA channel that appears to be critical to the
15 mediation of photic entrainment effects (cf. Colwell et al., 1990). This point is emphasized by
16 *in vivo* recordings from SCN cells in rats, in which we have shown that local APV
17 iontophoresis can block activation of SCN cells by NMDA and can also block activation of
18 these cells by sustained retinal illumination (R. Mason and B. Rusak, in preparation).

19 The identity of the native RHT transmitter remains uncertain. The dipeptide N-acetyl-
20 aspartyl-glutamate (NAAG) is found in retinal terminals in the SCN (Moffett et al, 1990) so
21 we investigated its effects and that of its two metabolites, N-acetyl-aspartate (NAA) and
22 glutamate. Glutamate, like NMDA, readily activates nearly all SCN cells, while NAA is
23 ineffective. By contrast, the effects of NAAG applications are quite variable. On different
24 SCN cells, NAAG had no effect, potentiated the effects of NMDA, or activated cells on its
25 own (M. Mirmiran, personal communication, 1992; R. Mason, H.D. Piggins and B. Rusak, in
26 preparation). The reason for this variability remains unclear. It may be that NAAG directly
27 affects an EAA receptor or that it is rapidly metabolized to form glutamate, which affects

1 receptors. A NAAG-specific dipeptidase has been identified in other parts of the brain,
2 including parts of the visual system (Slusher et al., 1992). If the dipeptidase were found in the
3 SCN, NAAG could be metabolized there to form glutamate after it is released from RHT
4 terminals. Whether the active agent is NAAG or glutamate, variable enzyme levels in different
5 slices may produce quite different results. We intend to pursue the issue by attempting to
6 correlate enzyme levels in SCN tissue with NAAG responsiveness.

7

8 FOS

9 To further examine the role of EAA receptors in transmission of photic information to
10 the SCN, we also took advantage of our previous findings that nocturnal light pulses stimulate
11 expression of *c-fos* and other genes in the hamster SCN (Rusak et al., 1990; see Kornhauser et
12 al., 1993 for review). We first showed that peripheral administration of the non-competitive
13 NMDA antagonist MK-801 (dizocilpine) can block photic induction of Fos immunoreactivity in
14 most regions of the SCN (Abe et al., 1991). We then used both systemic administration of
15 ketamine (a non-competitive NMDA antagonist) and intracranial injections of CPP and DNQX
16 (selective, competitive NMDA and non-NMDA antagonists) and found very similar results:
17 both NMDA and non-NMDA antagonists given before nocturnal light pulses suppress Fos
18 expression in large portions of the SCN (Abe et al., 1992). A role for both types of ionotropic
19 glutamate receptors in mediating light effects on Fos expression in SCN cells is consistent with
20 the hypothesis that non-NMDA activation functions as a gating mechanism for sustained
21 activation through the voltage-sensitive NMDA channel. Blockade of either channel could
22 prevent NMDA receptor-mediated Ca^{2+} influx, which may be critical to activation of gene
23 expression (Sheng and Greenberg, 1990).

24 Despite the efficacy of EAA antagonists in blocking Fos expression in most of the
25 hamster SCN, the dorsolateral portion of the caudal SCN continues to respond to nocturnal
26 retinal illumination with expression of Fos immunoreactivity (Abe et al., 1991; Ebling et al.,
27 1991). It is unlikely that this region simply does not get a sufficient dose of antagonist, since

1 the drug doses used are large, and the region is not normally particularly heavily labeled
2 compared to the rest of the SCN. Although immunocytochemical studies of transmitters in the
3 SCN have not indicated that this region is neurochemically distinctive (Card and Moore, 1984;
4 Morin et al., 1992), our results imply a transmitter/receptor system in this portion of the SCN
5 which differs from that operating in the remainder of the SCN. This difference might reflect
6 either a role for an EAA receptor which has not been blocked by the antagonists studied so far,
7 or for a different class of receptor which we have not yet identified.

8 One possibility we considered is that these cells may be activated indirectly via photic
9 activation of IGL cells which project using a non-EAA transmitter. Since we know that cells
10 projecting from the IGL to the SCN are light responsive (Harrington and Rusak, 1989; Zhang
11 and Rusak, 1989b), this hypothesis seems reasonable. We examined it by implanting
12 stimulating electrodes into the lateral geniculate region and testing whether stimulation can
13 activate Fos expression in the SCN. We found that stimulation there does activate SCN Fos
14 expression, and Fos immunoreactivity appears only in the dorsolateral portion of the caudal
15 SCN (Abe and Rusak, 1992). Although this result appears to confirm the hypothesis, it is not
16 obvious why activation via the GHT should be restricted to this area, given that the GHT
17 projects to all of the retinorecipient region of the hamster SCN (Harrington et al., 1985).

18 To further test the hypothesis that this activation represents IGL input to the SCN, we
19 have recently made knife cuts around the SCN to prevent input from caudal regions (including
20 the IGL) from reaching it, and in other animals we have made IGL/vLGN lesions, and then
21 given MK-801 and a light pulse. With MK-801 blocking activation in most of the SCN and
22 the lesions eliminating IGL input, we expected to see a complete lack of Fos in the SCN, yet
23 Fos-*lir* still appeared in the dorsolateral SCN.

24 An alternative explanation is that IGL stimulation can antidromically activate retinal cells
25 projecting to the IGL and that this activation is conveyed via the RHT back to a portion of the
26 SCN, resulting in dorsolateral Fos expression. We now have preliminary results suggesting
27 that ocular enucleations prevent the appearance of Fos-*lir* in the dorsolateral SCN after IGL

1 stimulations (H. Abe and B. Rusak, unpublished). Confirmation of these results would imply
2 the existence of a class of retinal ganglion cells influencing the IGL and dorsolateral SCN using
3 receptor mechanisms different from those operating in the rest of the SCN.

4

5 SEROTONIN

6 We have also begun a series of studies examining the role of serotonin (5-HT) in
7 modulating photic responses of SCN and IGL cells, and the receptor subtypes involved.
8 Serotonin and its interaction with light and the circadian system are of interest for several
9 reasons. First, there is a strong serotonergic projection from the raphe nuclei to both the SCN
10 and the IGL (see Meijer and Rietveld, 1989; Mantyh and Kemp, 1983). Second, both
11 serotonergic mechanisms and light are involved in some mood disorders (Skwerer et al.,
12 1988), and, finally, serotonin can have a potent phase-shifting influence on the SCN *in vitro*
13 and on behavioral rhythms (Edgar et al., 1993; Medanic and Gillette, 1992; Tominaga et al.,
14 1992).

15 In our first study, we showed that microiontophoretic application of either 5-HT or the
16 selective 5-HT_{1A} agonist 8-OH-DPAT to IGL cells in an anesthetized *in vivo* preparation
17 suppresses spontaneous firing activity during darkness and reduces the responses of these cells
18 to photic input (Zhang and Rusak, 1989a). We recently extended this study and showed that
19 suppression of IGL cell firing rates by these 5-HT agonists is dose-dependent and not
20 accompanied by changes in action potential waveforms. Co-application of the nonspecific
21 serotonin antagonist metergoline was effective in antagonizing the effects of both 5-HT and 8-
22 OH-DPAT. Furthermore, the selective 5-HT_{1A} antagonist, pindobind, when applied alone,
23 does not alter cell firing rates significantly, but it can antagonize the effects of 8-OH-DPAT on
24 IGL cell photic responses. These results suggest that 5-HT and 8-OH-DPAT act primarily
25 through a receptor subtype resembling the 1A receptor. Other putative 5-HT_{1A} antagonists,
26 pindolol, spiperone and propranolol, were either weak or ineffective in blocking the action of
27 8-OH-DPAT, although solubility problems might be limiting for pindolol in iontophoretic

1 experiments. Ketanserin, a 5-HT₂ antagonist and ritanserin, a 5-HT_{2/1C} antagonist, failed to
2 antagonize the effects of 5-HT on IGL cells (S.W. Ying, D.X. Zhang and B. Rusak,
3 manuscript submitted).

4 In addition, we have found that the pineal hormone melatonin suppresses both
5 spontaneous firing activity and photic responses of IGL cells in a dose-dependent manner.
6 Although melatonin is structurally similar to serotonin, these effects have not been reversed by
7 the 5-HT antagonists we have tested, suggesting mediation via a different receptor.

8 These results suggest a role for a 5-HT₁ receptor, similar to the 5HT_{1A} subtype, in
9 mediating serotonergic effects on IGL cells, although other subtypes may contribute to the
10 response. We are now examining the influence of 5-HT receptors on electrophysiological
11 responses of hamster SCN cells to light, and we have preliminary evidence that 8-OH-DPAT is
12 also effective in attenuating photic responses of these cells *in vivo* (S.W. Ying and B. Rusak,
13 unpublished).

14 15 SUMMARY

16 Our results indicate a role for EAAs and both NMDA and non-NMDA types of
17 receptors in mediating transmission of light information to the SCN. We have found evidence
18 that NAAG can play a role, but the nature of that role and the conditions under which NAAG
19 has its effects remain to be clarified. We have also shown that there is a retinal projection to
20 parts of the SCN which does not involve an EAA (at least not one we have yet successfully
21 antagonized), and tentative evidence that the retinal cells which project to this region also
22 project to the IGL. We hope to identify these cells, their projections, and their transmitters.
23 Finally, we have found that serotonin acting through a 5HT receptor which shares
24 characteristics with the 5HT_{1A} receptor, and melatonin acting through a non-serotonergic
25 mechanism, can alter photic responses of IGL and SCN cells. These results suggest
26 mechanisms by which serotonin and melatonin can modulate photic entrainment of the
27 mammalian circadian system. Our studies should help clarify the relations among the SCN, the

1 IGL and the raphe, and their contributions to the regulation of sleep, mood and circadian
2 rhythms.

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4

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